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## Review Article

# Mechanisms of aspirin-sensitive asthma

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### ABSTRACT

It is now widely accepted that aspirin, along with other non-steroidal anti-inflammatory drugs (NSAIDs), may precipitate asthma attacks in a minority of susceptible individuals. The syndrome is part of a mucosal inflammatory disease that typically affects the nasal, as well as the bronchial, mucosa and sometimes the gut and skin also. Although the mucosal cellular infiltrate in aspirin-sensitive asthma and rhinitis resembles that of asthma and rhinitis in general, there is evidence of increased expression of asthma-relevant cytokines, such as interleukin-5 and granulocyte-macrophage colony stimulating factor, and a more intense infiltrate of mast cells and eosinophils. One key feature of aspirin-sensitive asthma is thought to be the overproduction of cysteinyl leukotrienes, principally by these local mast cells and eosinophils, but whether this represents a fundamental abnormality or is simply a consequence of greater numbers and activation of inflammatory cells is unclear. Genetic polymorphisms of the leukotriene C<sub>4</sub> synthase gene, which result in elevated expression of this enzyme, may also play a role. In addition, overexpression of cysteinyl leukotriene receptors, particularly CysLT<sub>1</sub>, may contribute to an enhanced response of local inflammatory and structural cells to cysteinyl leukotrienes. Aspirin challenge in these patients is accompanied by acute further elevation of the already elevated baseline cysteinyl leukotriene synthesis, a phenomenon that is most closely related to the ability of aspirin and related NSAIDs to inhibit the cyclooxygenase enzyme COX-1. The reason for this is unknown, although it has been

suggested that the COX-1 product prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) serves as a 'brake' to leukotriene synthesis and that somehow this mechanism is deficient in aspirin-sensitive asthmatics. A better understanding of the pathogenesis of aspirin-sensitive asthma will undoubtedly lead to better approaches to treatment. Aside from the use of drugs that inhibit cysteinyl leukotriene synthesis or block the action of cysteinyl leukotrienes on their receptors, recent data suggest that PGE<sub>2</sub>, and possibly lipoxin analogs, may also prove effective in the treatment of aspirin-sensitive asthma.

**Key words:** aspirin-sensitive asthma, cyclooxygenase, cysteinyl leukotriene 1, leukotriene, prostaglandin E<sub>2</sub>.

### INTRODUCTION

The phenomenon of aspirin-sensitive asthma, first described by Widal *et al.*<sup>1</sup> and then extended by Samter and Beers,<sup>2</sup> is characterized by a syndrome of asthma and/or rhinitis precipitated by exposure to aspirin and related non-steroidal anti-inflammatory drugs (NSAIDs). Asthma, rhinitis or both may be prominent clinical features and the disease may also affect the mucosa of the gastrointestinal tract and the skin, causing gastrointestinal upset and urticaria/angioedema on aspirin exposure.<sup>3</sup> Aspirin sensitivity is seen in approximately 10% of adult asthmatics and commonly begins in middle age. The disease is slightly more common in females, but there is no relationship with the atopic diathesis.<sup>4</sup> Aspirin-sensitive asthmatics are over-represented in those presenting with life-threatening severe asthma attacks.<sup>5,6</sup>

Although the mechanism of aspirin sensitivity in asthma remains unclear, most investigators are agreed that the reaction to aspirin is not immunologically mediated. There is no evidence of an IgE response to aspirin and these patients do not have positive aspirin skin prick

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tests. The fact that the effect of aspirin is mimicked by a wide variety of other NSAIDs also makes the scenario of immunological cross-reactivity extremely unlikely. In addition, there appears to be no abnormality of bio-availability or metabolism of aspirin in these patients.<sup>7</sup> Because of this, the diagnosis of aspirin sensitivity can only be made objectively by experimental challenge. Current studies suggest that aspirin-sensitive asthma is most likely to be related to abnormal eicosanoid metabolism, both overproduction of the cysteinyl leukotrienes and increased expression of their receptors, and abnormalities of prostanoid metabolism, which may be further modified by drugs, such as aspirin, that inhibit cyclooxygenases. The purpose of this paper is to summarize the field to date based on studies in our own and other laboratories.

## ROLE OF CYSTEINYL LEUKOTRIENES

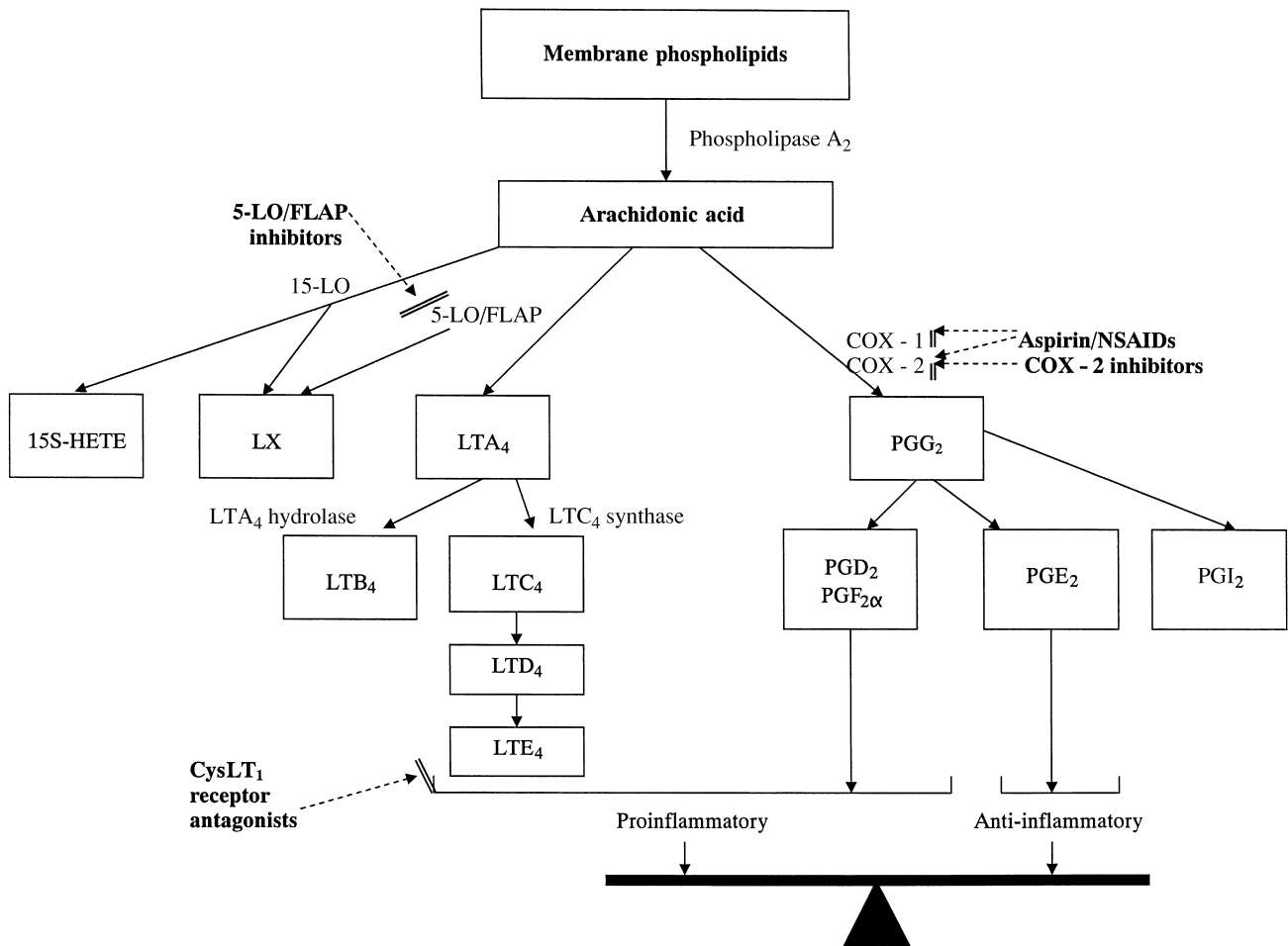
Cysteinyl leukotrienes are formed by the action of 5-lipoxygenase (5-LO) and 5-LO-activating protein (FLAP) on arachidonic acid released from cell membrane phospholipids by the enzyme phospholipase A<sub>2</sub> (Fig. 1). This produces leukotriene (LT) A<sub>4</sub>, which is hydrolyzed in neutrophils and monocytes to form LTB<sub>4</sub> and conjugated to glutathione in mast cells, basophils, eosinophils and other cells by the enzyme LTC<sub>4</sub> synthase to form LTC<sub>4</sub> and then enzymatically converted to LTD<sub>4</sub> and LTE<sub>4</sub>. The cysteinyl leukotrienes (LTC<sub>4</sub>/D<sub>4</sub>/E<sub>4</sub>) likely contribute to bronchoconstriction, microvascular leakage and elevated mucus secretion in asthma and rhinitis. Their role in regulating local mucosal inflammation is more controversial,<sup>8</sup> but probably contributory. It has been shown<sup>9</sup> that inhaled LTE<sub>4</sub> increases infiltration of eosinophils into asthmatic airways, although this effect is likely to be indirect because cysteinyl leukotrienes have little direct chemotactic activity for eosinophils *in vitro*. Although therapy with leukotriene receptor antagonists has been associated with a reduction in the numbers of bronchial mucosal eosinophils in asthmatics, this effect is not very marked in comparison with that of topical glucocorticoids.<sup>10</sup>

Increased production of cysteinyl leukotrienes is a characteristic of asthma in general, with increased concentrations of the relatively stable end metabolite LTE<sub>4</sub> found in the urine, bronchoalveolar lavage fluid and sputum of asthmatic patients.<sup>11</sup> We and others<sup>12,13</sup> have shown that aspirin-sensitive compared with -tolerant asthmatics have elevated urinary concentrations of LTE<sub>4</sub>

at baseline. In addition, this elevated baseline leukotriene production is further augmented for several hours following aspirin challenge.<sup>12–15</sup> A similar phenomenon is seen in the nasal mucosa of aspirin-sensitive patients.<sup>16,17</sup> We have also demonstrated reduction in the urinary concentrations of LTE<sub>4</sub> in aspirin-sensitive patients following successful aspirin desensitization.<sup>18</sup> Finally, we and others have shown that treatment of aspirin-sensitive asthmatics with leukotriene receptor antagonists results in improvements in lung function, symptoms and quality of life,<sup>19–21</sup> although the response is not dramatic and may be quite variable.<sup>22</sup> Furthermore, these drugs protect against acute aspirin challenge.<sup>23</sup> Taken together, these studies provide circumstantial, but very compelling, evidence for a role for the cysteinyl leukotrienes in regulating the severity of aspirin-sensitive asthma and that aspirin exposure, at least in the short term, exacerbates asthma in sensitive patients through elevated cysteinyl leukotriene production.

## ENHANCED PRODUCTION OF CYSTEINYL LEUKOTRIENES IN ASPIRIN-SENSITIVE ASTHMA: THE CHICKEN OR THE EGG?

Notwithstanding these observations, the question arises whether elevated cysteinyl leukotriene production is a cause, or a consequence, of increased bronchial mucosal inflammation in aspirin-sensitive asthma. There is some evidence that leukotriene synthesis is elevated in these patients *a priori*. For example, it has been reported<sup>24</sup> that the numbers of cells immunoreactive for LTC<sub>4</sub> synthase are significantly elevated in the bronchial mucosa of aspirin-sensitive compared with aspirin-tolerant asthmatics. There was some indication that this immunoreactivity reflected enzyme activity in the sense that a correlation was observed between the concentrations of cysteinyl leukotrienes in the bronchoalveolar lavage fluid of these patients and the numbers of LTC<sub>4</sub> synthase-immunoreactive cells. Furthermore, LTC<sub>4</sub> synthase expression in the aspirin-sensitive patients could be correlated with their bronchial responsiveness to soluble (lysine) aspirin challenge. In contrast, the total numbers of cells expressing immunoreactivity for 5-LO and FLAP, as well as LTA<sub>4</sub> synthase, were not different in the aspirin-sensitive and -tolerant patients. We similarly reported no significant difference in the total numbers of 5-LO-immunoreactive cells in aspirin-tolerant and -sensitive asthmatics.<sup>25</sup>



**Fig. 1** Outline of eicosanoid metabolism. The net effect of the prostanoids is to reduce asthma severity, whereas that of the cysteinyl leukotrienes (LTC<sub>4</sub>/D<sub>4</sub>/E<sub>4</sub>) is to increase it. This balance may be deranged in favor of increased leukotriene production and/or reduced production or activity of prostaglandin (PG) E<sub>2</sub> in aspirin-sensitive asthma. HETE, hydroxyeicosatetraenoic acid; LX, lipoxin; LO, lipoxygenase; FLAP, 5-lipoxygenase-activating protein; COX, cyclooxygenase.

Evidence has also been presented that the activity of enzymes involved in leukotriene synthesis, particularly LTC<sub>4</sub> synthase, may be genetically regulated. The -444A/C single nucleotide polymorphism allele, which lies in the promoter region of the LTC<sub>4</sub> synthase gene and may regulate its expression, has been associated with an elevated risk of aspirin-sensitive asthma in some studies,<sup>26</sup> but not in others.<sup>27</sup> In contrast, 30% of aspirin-sensitive asthmatics do not have this allele and it is expressed in 25% of aspirin-tolerant patients. Clearly, therefore, this allele alone does not represent a unique pathophysiological feature that separates aspirin-sensitive from -tolerant asthmatics. Other, as yet unidentified, genetic regulatory mechanisms may contribute. Similarly, although aspirin-sensitive asthmatics have elevated concentrations of

urinary LTE<sub>4</sub>, there is a broad overlap with tolerant patients, so that this cannot be used a diagnostic test.<sup>13</sup> There has been little study of the variability of leukotriene production in the general population (although such differences may only come to light in the context of inflammation). Finally, a single heritable gene abnormality resulting in abnormally elevated cysteinyl leukotriene production does not, in common with all similar genetic studies, readily explain why aspirin-sensitive disease may be acquired, at least clinically, late in life.

An alternative explanation for the overproduction of cysteinyl leukotrienes in aspirin-sensitive patients is that it reflects unique sensitivity of the cells that produce them, principally mast cells and eosinophils, to the effects of aspirin and other salicylates, including dietary salicylates.

Our own studies have demonstrated increased numbers of eosinophils and mast cells in the bronchial mucosa of patients with aspirin-sensitive asthma.<sup>25</sup> Furthermore, we have shown that, following segmental bronchial challenge of asthmatics with lysine aspirin, there is a significant reduction in the numbers of mucosal tryptase-positive mast cells in aspirin-sensitive compared with aspirin-tolerant asthmatics,<sup>28</sup> suggesting local direct activation and degranulation of mast cells. Such challenge was also associated with increased mucosal infiltration of activated eosinophils. Thus, direct activation of mast cells and eosinophils by salicylates, one of the consequences of which is elevated leukotriene production, may also play a role in the regulation of disease severity in aspirin-sensitive asthma. Surprisingly, the direct effects of aspirin on mast cells and eosinophils in these patients have been little explored.

Cytokines, particularly interleukin (IL)-5 and granulocyte-macrophage colony stimulating factor (GM-CSF), are involved in the activation, maturation and prolongation of survival of eosinophils. We reported previously that aspirin-sensitive compared with -tolerant asthmatics had significantly elevated numbers of bronchial mucosal mast cells and eosinophils expressing IL-5 and GM-CSF.<sup>29</sup> Other studies<sup>30</sup> have produced similar findings. This local enhanced production of eosinophil-active cytokines may also contribute to increased cysteinyl leukotriene production in aspirin-sensitive asthmatics. It has been shown, for example, that IL-5 enhances the synthesis of cysteinyl leukotrienes by eosinophils *in vitro*.<sup>31</sup>

In view of all these observations, the question whether or not aspirin-sensitive asthma is associated with a fundamental, predetermined abnormality in the production of cysteinyl leukotrienes, as opposed to being merely an expression of particularly severe disease caused by unique sensitivity of granulocytes, such as mast cells and eosinophils to aspirin exposure, remains open. These possibilities are not, of course, mutually exclusive.

## CYSTEINYL LEUKOTRIENE RECEPTORS IN ASPIRIN-SENSITIVE ASTHMA

The leukotrienes exert their actions on inflammatory cells, mucosal capillaries, mucus glands and smooth muscle by interacting with specific receptors. G-Protein-coupled receptors for LTB<sub>4</sub> and the cysteinyl leukotrienes have been characterized separately. So far, two receptors for the cysteinyl leukotrienes, termed CysLT<sub>1</sub> and CysLT<sub>2</sub>, have been cloned.<sup>32,33</sup> Both receptors bind to

LTC<sub>4</sub>, LTD<sub>4</sub> and LTE<sub>4</sub> with affinity order LTD<sub>4</sub> > LTC<sub>4</sub> >> LTE<sub>4</sub> (CysLT<sub>1</sub>) and LTD<sub>4</sub> = LTD<sub>4</sub> >> LTE<sub>4</sub> (CysLT<sub>2</sub>) and both are expressed on bronchial smooth muscle cells and inflammatory leukocytes. Because CysLT<sub>1</sub> receptor antagonists ameliorate basal and aspirin-provoked asthma in aspirin-sensitive asthmatics, it seems very likely that at least some of the disease regulatory actions of the cysteinyl leukotrienes are mediated through this receptor. In a recent study,<sup>34</sup> we showed that the total number of cells, as well as the percentages of total inflammatory leukocytes expressing the CysLT<sub>1</sub> receptor, was significantly elevated in the nasal submucosa of patients with aspirin-sensitive compared with aspirin-tolerant chronic rhinosinusitis. In contrast, the percentages of total leukocytes expressing the LTB<sub>4</sub> receptor did not differ significantly between the two groups. We also found that topical nasal desensitization of the aspirin-sensitive patients was associated with a reduction in the numbers of nasal inflammatory cells expressing CysLT<sub>1</sub>. These observations importantly suggest that, in addition to overproduction of cysteinyl leukotrienes, aspirin-sensitive asthma may also be associated with overexpression of the CysLT<sub>1</sub> receptor. This may result in an increased sensitivity of aspirin-sensitive asthmatics to the effects of exogenous leukotrienes. For example, inhaled LTE<sub>4</sub> increases bronchial inflammation in asthmatics<sup>9</sup> and this process may be further augmented in aspirin-sensitive asthma if the responding inflammatory cells overexpress CysLT<sub>1</sub>. We have shown<sup>35</sup> that aspirin-sensitive asthmatics are hyperresponsive compared with tolerant patients to the bronchoconstrictor effects of inhaled LTE<sub>4</sub>. Again, this may putatively reflect overexpression of cysteinyl leukotriene receptors on bronchial smooth muscle in these patients. It will be vital to extend these studies on rhinosinusitis to the bronchial mucosa of aspirin-sensitive and -intolerant asthmatics. Such studies are now in progress in our department.

The CysLT<sub>2</sub> receptor resembles the CysLT<sub>1</sub> receptor in terms of its ability to mediate calcium influx in transfected cells and binds to all three cysteinyl leukotrienes with similar affinity (see above). Although characterized pharmacologically predominantly so far on human pulmonary venous smooth muscle, previous studies suggest that the CysLT<sub>2</sub> receptor is also expressed in lung parenchyma, as well as on inflammatory leukocytes.<sup>33</sup> Our preliminary studies of the nasal submucosa of patients with aspirin-sensitive rhinosinusitis showed clear expression of the CysLT<sub>2</sub> receptor on inflammatory leukocytes,

epithelial cells and glands, although, in contrast with CysLT<sub>1</sub>, expression of CysLT<sub>2</sub> was not significantly different in the aspirin-sensitive compared with -tolerant patients. Nevertheless, these observations suggest a possible role for CysLT<sub>2</sub> receptors in mediating some of the disease regulatory effects of cysteinyl leukotrienes in aspirin-sensitive asthma and, indeed, in asthma in general. This may encourage the further development of drugs such as BAY u9773, which antagonizes both CysLT receptors.

A final small enigma relates to the actions of exogenous leukotrienes on asthmatic subjects *in vivo*. As mentioned, we have shown<sup>35</sup> that aspirin-sensitive asthmatics show bronchial hyperresponsiveness to LTE<sub>4</sub>, but not LTD<sub>4</sub> or LTC<sub>4</sub>. Other studies<sup>9</sup> have similarly shown that inhaled LTE<sub>4</sub>, but not LTD<sub>4</sub>, increases bronchial inflammation in subjects with asthma. In view of the pharmacologically defined differential sensitivity of both the CysLT<sub>1</sub> and the CysLT<sub>2</sub> receptors for LTC<sub>4</sub>/D<sub>4</sub>/E<sub>4</sub> ligands (see above), it is difficult to understand why LTE<sub>4</sub>, but not LTD<sub>4</sub> or LTC<sub>4</sub>, produces such effects if they are mediated through the CysLT<sub>1</sub> or CysLT<sub>2</sub> receptors. One may speculate that inflammation may have altered post-receptor signaling, resulting in differential regulation in a ligand-specific fashion. Alternatively, it is possible that there are further cysteinyl leukotriene receptors that remain to be discovered.

## ROLE OF PROSTANOIDS IN ASPIRIN-SENSITIVE ASTHMA

Arachidonic acid is a substrate for the production of both leukotrienes and prostanoids (Fig. 1). Prostanoids are manufactured by the enzyme cyclooxygenase (COX), which exists in two isoforms, termed COX-1 and COX-2, which are encoded by distinct genes. Both enzymes conjugate with a peroxidase to form the enzyme prostaglandin H<sub>2</sub> (PGH<sub>2</sub>) synthase. Cyclooxygenase inhibitors prevent this association. Cyclooxygenase-1 is expressed constitutively in most mammalian cells and is probably responsible for the physiological production of prostanoids that regulate many normal body processes. In contrast, COX-2 is inducible and is generally expressed only in the context of ongoing inflammation. We<sup>36</sup> and others<sup>24,37</sup> have shown that the numbers of cells showing immunoreactivity for COX-2 are increased in the bronchial mucosa of asthmatics compared with controls, but that COX-2 expression is not particularly elevated in aspirin-sensitive compared with -tolerant asthmatics, either at baseline or following aspirin challenge.

The ability of drugs to exacerbate symptoms in aspirin-sensitive asthmatics is directly related to their COX-1 inhibitory activity.<sup>38,39</sup> Inhibitors of COX-1 induce acutely elevated local and systemic leukotriene release in these patients.<sup>14,18,40</sup> The time-honoured but somewhat naïve concept that COX-1 inhibitors 'divert' arachadonic acid metabolism away from prostanoid synthesis and towards leukotriene synthesis has been refined. In particular, there is good evidence for a specific role for the prostanoid PGE<sub>2</sub> in ameliorating aspirin-induced asthma. For example, in these patients, exogenous PGE<sub>2</sub> blocks aspirin-induced bronchoconstriction, elevated urinary LTE<sub>4</sub> concentrations and release of cysteinyl leukotrienes from cultured peripheral blood leukocytes.<sup>41,42</sup> Prostaglandin E<sub>2</sub> also regulates 5-LO activity<sup>43</sup> and inhibits mast cell degranulation. In animal 'models' of asthma, targeted deletion of the COX-1 or COX-2 genes increases inflammatory influx into the airways following ovalbumin challenge, again underlining the significant role of COX-1/2 products in limiting airway inflammation.<sup>44</sup> Some products of COX-1/2, such as PGD<sub>2</sub> and PGF<sub>2α</sub>, are in contrast proinflammatory, or at least cause bronchoconstriction, so presumably these effects reflect a summation of the action of several, potentially antagonistic prostanoids.

Inhibition of COX-1, leading to reduced PGE<sub>2</sub> production, thus constitutes one mechanism for COX-1 inhibitor-induced exacerbation of asthma, but the key question is why this phenomenon is not observed in all asthmatics, but only in those who are aspirin sensitive. It is possible to speculate that the COX enzymes are differentially susceptible to aspirin inhibition in aspirin-sensitive and -tolerant patients, but there is no evidence for a mechanism for this and no evidence of polymorphism of the relevant genes. Alternatively, aspirin and related drugs may have other effects on the COX enzymes not directly related to the inhibition of the production of prostanoids.<sup>45</sup> Another possibility is that the COX-1/2 enzymes are the same in aspirin-sensitive and -tolerant asthmatics, but the former patients are particularly dependent upon the tonic inhibition of cysteinyl leukotriene generation by the action of PGE<sub>2</sub> on target cellular receptors. This may reflect a relative deficiency of PGE<sub>2</sub> production, abnormality of PGE<sub>2</sub> receptor expression or both. There are two studies in the literature suggesting that PGE<sub>2</sub> production may be deficient in aspirin-sensitive patients. In the first,<sup>46</sup> epithelial cell monolayers outgrown using hormones from resected nasal polyps produced slightly but significantly less PGE<sub>2</sub> after 6 days of culture *in vitro* in aspirin-sensitive

compared with -tolerant patients. In the second study,<sup>47</sup> fibroblasts outgrown from bronchial biopsies (2–3 weeks of culture) produced less PGE<sub>2</sub> in response to 18 h of stimulation with cytomix (lipopolysaccharide/IL-1 $\alpha$ /tumour necrosis factor- $\alpha$ ) in aspirin-sensitive compared with -tolerant patients, although spontaneous production was equivalent. In both studies, cells from aspirin-sensitive and -tolerant patients showed no differential sensitivity to suppression of PGE<sub>2</sub> production by exogenous COX-1 inhibitors. Consequently, the evidence that aspirin-sensitive asthmatics are deficient in PGE<sub>2</sub> synthesis, or that this process is more susceptible to aspirin inhibition in aspirin-sensitive patients, is currently limited. Furthermore, the hypothesis that PGE<sub>2</sub> deficiency is a fundamental problem in aspirin-sensitive asthma does not sit well with the observation that selective COX-2 inhibitors, which presumably also reduce PGE<sub>2</sub> production,<sup>48</sup> do not appear to increase leukotriene production and bronchospasm in these patients.<sup>49</sup> As an alternative to the deficient production of PGE<sub>2</sub>, an alternative hypothesis is that these patients may show a deficiency of PGE<sub>2</sub> receptor expression on target leukocytes and other tissues, which may result in deficient PGE<sub>2</sub> 'braking' of cysteinyl leukotriene production at baseline, which is further exaggerated by COX-1 inhibition.

There are four G-protein-coupled PGE<sub>2</sub> receptors designated EP<sub>1–4</sub>.<sup>50</sup> Whereas EP<sub>2</sub> and EP<sub>4</sub> receptors activate adenylate cyclase and increase cAMP, EP<sub>3</sub> generally couples to G<sub>i</sub> and reduces cAMP, although recently described splice variants of EP<sub>3</sub> may conversely elevate cAMP in the presence of high concentrations of agonist.<sup>51</sup> Thus, there is plenty of scope for variability in the responses of target cells to PGE<sub>2</sub> according to the spectrum of receptors they express. The receptors EP<sub>1</sub>, EP<sub>3</sub>, and EP<sub>4</sub> are widely expressed in human cells, including inflammatory leukocytes, mast cells and smooth muscle.<sup>50,51</sup> There are very few reports addressing the expression of PGE<sub>2</sub> receptors on inflammatory leukocytes in the human lung and, as yet, none in the context of aspirin-sensitive asthma. In a preliminary study of nasal biopsies from patients with aspirin-sensitive chronic rhinosinusitis, we have obtained unequivocal evidence of staining with antibodies to all four EP receptors. The cells stained included leukocytes, glandular cells, epithelial and endothelial cells, with a clearly distinct staining pattern in each case. In these sections, we noted increased global expression of EP<sub>1</sub> and EP<sub>2</sub>, but not EP<sub>3</sub> and EP<sub>4</sub>, in the nasal mucosa of patients with rhinosinusitis compared with controls, although there were no

significant differences at this level between aspirin-sensitive and -tolerant subjects. Examination of receptor expression on individual inflammatory cells is, at present, in progress.

## OTHER PRODUCTS OF THE LIPOXYGENASE PATHWAYS

Apart from leukotrienes, there are other recognized products resulting from the action of lipoxygenase enzymes. The best described are 15S-hydroxyeicosatetraenoic acid (15S-HETE) and the lipoxins (LX). 15S-Hydroxyeicosatetraenoic acid is generated by direct metabolism of arachidonic acid by 15S-LO, whereas LX are double lipoxygenase products formed through the enzymatic action of both 5-LO and 15-LO. There is little information about the role of 15S-HETE in asthma, although there is increasing interest in the biology of the LX.<sup>52</sup> A recent report suggests that peripheral blood leukocytes, when exposed to aspirin, produce more 15S-HETE in aspirin-sensitive compared with aspirin-tolerant, patients.<sup>53</sup> Conversely, the production of LX and 15-epimer LX was elevated in aspirin-tolerant compared with -sensitive asthmatics.<sup>54</sup> This suggests that LX may be 'protective' or 'anti-inflammatory'. Further support for this idea has come from a murine model of asthma with transgenic leukocyte expression of human LXA<sub>4</sub> receptors. In this model, administration of a stable LXA analog blocked allergen-induced airway responsiveness and inhibited lung inflammatory cell infiltration and local cytokine, as well as prostanoid and cysteinyl leukotriene production.<sup>55</sup> Studies in humans with LX analogs are now needed to further define the role of these potentially important eicosanoid mediators in aspirin-sensitive asthma and, indeed, in asthma in general.<sup>56</sup>

## IMPLICATIONS FOR FUTURE MANAGEMENT

Despite the strong scientific rationale for the use of antileukotriene drugs in aspirin-sensitive asthma, these have not had the impact on day-to-day therapy of these patients that may have been expected. Although several clinical trials have confirmed that they improve lung function and quality of life, there is a variability of response between patients.<sup>19–22</sup>

With the advent of highly selective COX-2 inhibitors, which appear, so far, to be relatively safe in aspirin-sensitive asthmatics,<sup>49</sup> a requirement to tolerize these patients to aspirin so that they can receive aspirin and

related COX-1 inhibitors for their anti-inflammatory and analgesic effects has become less of a priority (although it should be noted that COX-2 inhibitors do not exert the antiplatelet effects of aspirin and, therefore, are not suitable for the prophylaxis of stroke or myocardial infarction).

As a therapeutic strategy, aspirin desensitization still bears scrutiny. In a typical desensitization regimen, small incremental oral doses of aspirin are ingested over the course of a few days until 650 mg aspirin is tolerated. This dose is then maintained daily. If doses are increased still further, typically to 650 mg twice daily, patients often experience some improvement in their chronic asthma and rhinitis. In a recent long-term study of patients treated in this manner,<sup>57</sup> after 1 year of continuous aspirin treatment patients experienced highly statistically significant, but clinically rather small, improvements in nasal symptoms and requirements for inhaled and topical nasal corticosteroid doses. There was a more useful reduction in exposure of these patients to short courses of oral prednisolone for asthma exacerbations. Approximately one-third of patients 'failed' desensitization, either because of the development of intolerable unwanted effects or because the procedure was ineffective.

Given that the precise mechanism of aspirin intolerance is unknown, it is no surprise that the precise mechanism of aspirin desensitization is also very unclear. We<sup>18</sup> have shown that desensitization does not completely abrogate production of LTE<sub>4</sub> detectable in the urine, but does blunt the acute asthmatic response to further aspirin challenge. Aspirin desensitization also reduces bronchial responsiveness to exogenous leukotriene, a phenomenon that may reflect, at least partly, downregulation of CysLT<sub>1</sub> receptors on mucosal inflammatory cells (see above).<sup>34</sup> Finally, it should not be forgotten that aspirin is a potent anti-inflammatory drug in its own right and very high doses of aspirin may exert other anti-inflammatory effects on the asthma process: for example, it has been shown that aspirin can inhibit the activation of signal transducers and activators of transcription (STAT) 6 by IL-4 and IL-13 *in vitro*.<sup>58</sup>

In view of our preliminary evidence for the expression of both CysLT<sub>1</sub> and CysLT<sub>2</sub> receptors in the respiratory mucosa of patients with aspirin-sensitive rhinosinusitis and given the fact that CysLT<sub>2</sub> receptors have already been implicated in mediating some of the effects of the cysteinyl leukotrienes on tissue such as airways smooth muscle,<sup>59</sup> there may be a rationale, as mentioned previously, for the further development of combined antagonists of both CysLT<sub>1</sub> and CysLT<sub>2</sub> receptors, such as

BAY u9773. Against this is the observation that treatment of aspirin-sensitive asthmatics with 5-LO inhibitors, which should theoretically completely prevent the production of cysteinyl leukotrienes and, thus, obviate the problem of blocking leukotriene receptors, has not shown such remarkable clinical advantages as may have been expected over the CysLT<sub>1</sub> leukotriene receptor antagonists,<sup>60</sup> although a recent trial<sup>61</sup> showed that treatment of patients with the 5-LO inhibitor zileuton produced improvement in nasal symptoms and improved non-specific bronchial hyperresponsiveness, as well as aspirin-induced bronchoconstriction.

Looking slightly further into the future, it is possible that stable analogs of inhibitory prostanoids, such as PGE<sub>2</sub>, as well as LX, may also prove useful for the treatment of aspirin-sensitive asthma.

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